

## ENCEPHALOPATHY AND NEUROENDOCRINE DISORDER IN SEPTIC SHOCK

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### ABSTRACT

*Infection by pathogenic microorganisms triggers an acute phase response which manifests itself with fever, neuroendocrine changes and behavioral changes. Sepsis induced early impairment of neuronal metabolism and activity. Septic encephalopathy is a severe brain dysfunction caused by systemic inflammation in the absence of direct brain infection. Sepsis enhanced the transcription of several pro- and anti-inflammatory cytokines and chemokines including TNF- $\alpha$ , IL-1 $\beta$  and TGF- $\beta$  in the cerebrum. Activated microglia during sepsis could play a role in behavioral changes associated with systemic infection. Changes in cerebral blood flow, release of inflammatory molecules and metabolic alterations contribute to neuronal dysfunction and cell death.*

**Keywords:** encephalopathy, neuroendocrine, Sepsis

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### INTRODUCTION

Sepsis is the most cause of death in the world, and as the cause of the highest in the patients in the Intensive Care Units (ICU), which incidence increased (Shahin et al. 2006). Up to 70% of patients sepsis may potential to develop into organs cerebral aberration function in acute (acute Cerebral dysfunction) (Wilson & Young 2003). This is the clarity that septic shock can be associated with damage or aberration function cerebral (Sharshar et al. 2004).

The state of sepsis can trigger the occurrence of encephalopathy. Encephalopathy septic including sepsis into the clear, because in the sepsis is caused by the existence of systemic inflammation where the infection does not get the brain directly and obtained the characteristic clinical signs of a slowing of mental processes, which decreases awareness, disorientation, delirium and coma occur. And, most importantly that septic encephalopathy (SE) is an early sign of sepsis and associated with increased mortality and morbidity (Semmler et al. 2008).

SE Pathogenesis conditions such as sepsis is not directly triggered by pathogenic toxin, in the SE this encephalopathy can develop as a result of the Systemic inflammatory Response Syndrome (SIRS), which causes the infection not found. Information from the experiment and clinic seen a number of factors such as cytokine pro-inflammation local, microcirculation

cerebral weakness, imbalance neurotransmitter and the negative influence of organ peripheral failure contribute to an SE. Moreover, there is a settling of inflammation may cytotoxicity increase stress and oxidative further SE may cause a more severe, than that also play a role in the occurrence of deviation or slowdown neuronal function. Patients who have conditions pathologic on the central nervous system have previously may higher risk of going for the SE, and similar things can also be seen in an animal model of sepsis. Reciprocal interaction between the system behind the central nervous system and immunity is now considered as the main components of the host responds in shock septic.

Sepsis pathophysiology is a result of complex interactions between the infection of pathogenic bacteria, inflammation and the coagulation is characterized as imbalance between cytokine proinflammation with cytokine anti-inflammation (Kristine et al. 2007).

Reciprocal interaction between the system behind the central nervous system and immunity is now considered as the main components of the host responds in shock septic. Central nervous system is part of a special, because muscle is part of the immunity system such as the blood-brain barrier (BBB), the system lymphatic and parenchymal cells that play a role in expression of the complex with the antigen molecules major histocompatibility complex (MHC). Central nervous system to set up a wide physiological functions that are very important in the maintenance of homeostasis and

the setting of a complex host response to the level of autonomy, neuroendocrine and behavior. There is interference from some function adaptive will affect the shock septic. Need to be reviewed so that the brain areas involved in the response to infection, and the mechanism of interaction between brain and immunity during the shock septic, and clinical aspects of the aberration function cerebral the shock septic.

## NEUROPATHOLOGY OF SEPTIC SHOCK

From the results of the research results indicate that autopsy of patients who died due to shock septic shows all visible ischemic lesion cases, bleeding (26%), hypercoagulability syndrome (9%), microabscess (9%), and multifocal necrotizing leucoencephalopathy (9%) related with the local expression of pro-cytokine and inflammation high degree cytokine pro-inflammation in circulation (Sharshar et al. 2004). This result shows that the central nervous system solely through the process can be broken inflammation, compared hypoperfusion or interference during coagulation shock septic (Sharshar et al. 2002).

## IMMUNITY-CENTRAL NERVOUS SYSTEM CHANNEL

Immunity system is a system that is sensory may provide signal the existence of microorganisms to the central nervous system through three main channels.

1. Circumventricular organs, which consists of a network and occupies a special bundle that strategic location. Because they are not protected by BBB, functioned as the structure of communication between the brain blood vessels (Goehler et al. 2000).
2. Vagal nerve, as the sensor inflammation in peripheral (through receptor cytokine located on the surface of the nerve), will convey information to the immunity and then medulla may inflammation pressing on the side of infection (through receptor nicotinic acetylcholine in the monocyte) (Wang et al. 2003).
3. Activation and leakage endothelium, which will cause the release and diffusion passive mediator-mediator inflammation and neurotoxic (Tarek et al. 2005).

## BLOOD-BRAIN BARRIER DURING INFECTION

Results of the experiment in both the animal and try to show the human cytokine and lipopolysaccharide (LPS) both in peripheral and directly into the brain will be able

to make changes and behavioral disturbances (Dantzer 2004). Results from several observations indicate microglial cells plays an important role in the changes mediating behavior of the systemic infection (Lemstra et al. 2007). Cytokine pro-inflammation and LPS trigger the expression of CD40, vascular adhesion molecule-1 or intercellular adhesion molecule-1, and E-selectin on the cell endothelial-vessel blood vessel in the brain (Omari & Dorovini-Zis 2003). It also causes the activation of genes transcript codes of cyclooxygenase-2 (Cox-2) and stimulate path I? B/NF-? B. Although cells endothelial in the brain do not express CD14 on the surface, LPS is also able to trigger cascade mitogen-activated protein kinase through a soluble CD14. Cells of the brain activated endothelial LPS may receptor express IL-1 and TNF- $\alpha$ ; Produce IL-1, TNF- $\alpha$  and IL-6; and secretes endothelial and inducible nitric oxid synthase (eNOS and iNOS) (Tarek et al. 2005). Mediators will interact with surrounding brain cells that will cause the response inflammation. This activation endothelium may BBB changes, so that there will be a deviation function cerebrovascular. Nitric oxide (NO), prostaglandin and cytokine set neurotransmission brain, especially system-Adrenergic, production and release CRF, ACTH and vasopressin. Instead, neurotransmitter and neurohormone also set cerebral expression of mediator-mediator inflammation. (Dunn 2000; Matsuoko et al. 2003).

Most important aspect of apoptosis is cerebral dysfunction of brain cells, with the finding apoptosis cells and nerve microglia on hypothalamus and autonomous center in the brain of cardiovascular patients who died because of shock septic. Apoptosis of brain cells occurs as a consequence of various factors that play a role during shock septic including ischemia, glial cell activation, TNF- $\alpha$ , IL-1, Interferon-gamma and NO (Yuan & Yankner 2000). At intracellular, activation or retardation mitochondrial respiration, activation mitogen-activated protein kinase pathways and NF-1B, and release agents cytotoxic as calcium and reactive oxygen species (Ros) will be able to protect against heat shock proteins (Brealey et al. 2002).

## SEPTIC ENCEPHALOPATHY

Encephalopathy on the prevalence of severe sepsis varies from 9% to 71%, depending on the level of severity based on clinical criteria, electroencephalographic (EEG) and its potential sensoric (Zauner et al. 2002). Where is the illness of this encephalopathy may disease associated with illness in general, its septic score (Acute Physiology and Chronic Health Evaluation II score / Apache score or the score from the organ failure), and its mortality. Many factors

that affect the pathophysiology of encephalopathy, including among others:

- a. Cerebral endothelial dysfunction may that result in a decrease Cerebral blood flow and BBB, increased translocation molecule-molecule neurotoxic and ischemic or hypoperfusion of the brain.
- b. Increasing the degree of amino acid neurotoxic (such as Amonium, tyrosin, triptophane and phenilalanine) in blood plasma, because of sepsis occur in the processes of reduction and proteolytic function of the liver.
- c. Inflammatory mediators and endotoxin, which will lead to changes in cell metabolism and neuron-glia cells. So that the failure of kidney function and the liver, metabolic interference and the drugs that are neurotoxic may exaggerate speed and the occurrence of brain dysfunction (Tarek et al. 2005). Neurone-specific enolase is a sign of lesion in the brain, so it can be used as death predictor in septic-shock patients (Weigand et al. 2000).

## NEUROENDOCRIN INTERFERENCE

Response endocrin in sepsis is complex, in general, the severe sepsis that has been a disruption in the hypothalamic-pituitary path-adrenal, in which sepsis occurs insufficiency adrenal may lead to a decrease in the sensitivity of the blood vessel vasopressors and increased risk of death. So that more of the shock cortisol may septic improve interference, this will increase its hemodynamic and survival. (Tarek et al. 2005).

Development of therapy with drugs will impact on the fundamental morbidity and sepsis mortality. The concept of modulation inflammation systemic response to sepsis caused a lot of heavy drugs anti-inflammation used in clinical trials. The provision of anti-endotoxin anti-CD14, anti-LBP, anti-platelet activating factor, anti-TNF, and anti-IL-1 does not show all of the improvement of life of sepsis. (Guntur 2008). Conversely, activated protein C, low dose corticosteroid, and intensive insulin therapy is able to reduce mortality has been proved and have started to receive patients management shock septic. So that the current research is to see growing levels of drug-drug interaction in the apoptosis pathways in the immune system (Wesche-Soldato et al. 2007).

Use corticosteroid as early as possible management recommended in sepsis, acute lung injury, acute respiratory distress syndrome and refractory vasodilatory shock (Aberdein & Singer 2006). From the results of the meta-analysis of research using high-dose steroid short term is not recommended in management

shock septic, but recommends the use of low dose corticosteroid long-term (equivalent to 200 to 300 mg per day hydrocortison) (Annane et al. 2002). This is by opinion, which states that high-dose corticosteroid may pressing immune system, while increasing low-dose immune system. On the other studies reveal corticosteroid use as early as possible will increase the frequency of infection nosocomial, polymicrobial infection and fungus infection during treatment in the hospital. So corticosteroid may increase the risk of death or disability in patients with acute critical illness. (Rady et al. 2006).

Catching the point of low-dose corticosteroid in sepsis, the response is inflammation systemic, as vasopressor, cytokine prevent the production pro-inflammation, preventing production of mediators, mediators inflammation as cyclooxygenase-2, lower leucocyte adhesion to the endothelium (Annane & Caillon 2003; Rhen & Cidlowski 2005).

## CONCLUSION

Shock septic often leads to complications such as encephalopathy, neuroendocrine interference and failure cardiovascular a bad impact on the patient's sepsis. Interference mechanism is very complex and a clear signal mismatch occurs between the brain and immunity, which will generate activation brain cells, NO production disruption, dysfunction metabolism intracellular and cell death either via the necrosis and apoptosis.

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